II. REMARKS

Claims 56 to 79, 81-84 and 86-89 are pending in the subject application and stand variously rejected by the Office in the outstanding Office Action. By this Amendment and Response, claims 58, 71, 72 and 80-85 have been canceled and claims 56, 57, 59-62, 86 and 87 have been amended.

These amendments are made without prejudice or disclaimer and are not intended to be a dedication to the public the subject matter of the claims or their equivalents, as filed or previously amended. Applicants reserve the right to pursue the claims as originally filed and previously amended in a later filed continuation application.

The amendments were not made earlier as it is Applicants' belief that the claims as previously presented describe allowable subject. However, these amendments are now being made in a sincere effort to advance allowance of the claims or to put them in better form for consideration an appeal.

Support for the amendments to the claims can be found in the specification as originally filed. An issue of new matter is not raised by these amendments and entry thereof is respectfully requested.

In view of the preceding amendments and remarks that follow, reconsideration and withdrawal of the objections to the specification and the rejections of the claims are respectfully requested.

Examiner Interview

Applicants' attorney thanks the Office for the courtesy extended to them during the preceding telephonic interview. The rejection of the claims under 35 U.S.C. § 112 were discussed and possible language to overcome the grounds for rejection. The Office's suggested language discussed during this interview is reflected in this amendment and reply.

Related Case

The Examiner requested a copy of the pending claims of U.S. Serial No. 10/048,033. A copy of the claims is enclosed for the Examiner's convenience.

35 U.S.C. § 112, First and Second Paragraphs

Claims 56 and 57 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Office asserted that claims 56 and 57 are directed to methods of inhibiting and treating wherein the particular disease to be treated has not been specified, the particular active ingredients have not been defined, and the host has not been defined by the functional terms "phosphoramidatyl prodrug" and "hyperproliferative neoplastic cell(s)."

The Office referred Applicants to the newly cited PTO-892 references SA (Stedman's Medical Dictionary) and TA (Merck Manual). The Office argued that in light of the minimal nature of the instant disclosure, the Office does not agree with Applicants' claims which represent an extrapolation based on only the single instant example of antineoplastic disease treatment to the encompass the generic class of all neoplastic conditions. The Office requested a more comprehensive showing of efficacy against a broad range of different cancers *in vitro* or *in vivo* in support of the claims.

Claims 56-61, 81-84 and 86-89 also stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly containing subject matter which was not described in the specification in such a way as to enable one of ordinary skill in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 62-79 also stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly containing subject matter which was not described in the specification in such a way as to enable one of ordinary skill in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 56-59, 61-63, 65, 72, 81-84 and 86-87 stand rejected under 35 U.S.C. § 112, second paragraph, for allegedly failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

In claims 56 and 57 the Office remarked that the term "a 5'-phosphoryl or phosphoramidatyl prodrug of a 5- substituted pyrimidine nucleoside or nucleotide, a derivative or a metabolite thereof" fails to completely define the structural metes and bounds of the claims. The Office also stated that in light of the initial requirement of a "5'-phosphoryl or phosphoramidatyl" substituent it is also unclear where the additional "phosphate" group(s) are located as required by the included term "nucleotide." The Office also noted claim 58, wherein the terms "prodrug," "derivative," and "metabolite" also appear at lines 1-2.

In claim 57 at line 1, the Office objected to the term, "hyperproliferative neoplastic cells" for allegedly failing to specify the particular disease being referred to.

Claim 58 also was rejected on various grounds set forth on page 7 of the Office Action. Without conceding the correctness of the Office's position, the claim has been canceled without prejudice or disclaimer thereby obviating these grounds of rejection.

Claim 59 is allegedly indefinite for failure to provide the structural details for the chemical species ("masked phosphoryl moiety" and "phosphoramidatyl moiety").

In claim 62 at lines 10-11, the Office objected to the term "aromatic hydrocarbyl" on the ground the term lacks size limits and therefore render the instant compound indefinite for failure to provide adequately defined structural metes and bounds. Also, the term "heteroaromatic" is incompletely defined for failure to define the identity or limits on the proportion of the heteroatom or heteroatoms present.

Applicants respectfully traverse. In response to the Office's rejections, but without conceding the correctness of the Office's position, claims 56 and 57 are amended to recite that the claimed methods are particular to cells that endogenously overexpress thymidylate synthase. Support for this amendment to the claims found throughout the specification, and in particular, page 13, lines 15 to 29. Claims 58, 71, 72 and 80 through 85 are now canceled without prejudice or disclaimer.

Claims 56, 57, 59, 60, 61, 62, 68, 86 and 87 have been amended in a sincere effort to address and overcome the grounds for rejection. The claim amendments were discussed with the Office during the March telephonic interview. Support for the amendments to claims 56, 57, 59 and 62, as they relate to overcoming the stated

grounds for rejection can be found in the application papers on pages 40; 41; 46 line 13 to page 47, line 5, page 57, line 2 to line 20; and page 73, line 13 to page 74, line 5. Applicants also have amended claim 62 to insert the limits on the proportion of the heteroatom present in the claim. Support for the amendment is found on page 41, lines 1 to 5.

Applicant believes the preceding amendments to the claims address and overcome all outstanding rejections raised under 35 U.S.C. § 112, first and second paragraphs. Reconsideration and withdrawal of the rejections is therefore respectfully requested.

Double-Patenting

Claims 56-61, 81-84 and 86-89 remain rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-12 of U.S. Patent No. 6,495,553.

Claims 62-80 remain rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 36-39 of U.S. Patent No. 6,339,151.

Claims 56-84 and 86-89 remain rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-7 of U.S. Patent No. 6,245,750 and claims 1-30 of co-pending application Serial No. 10/119,927.

Claims 56-61 and 81-89 stand rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-22 of co-pending U.S. Serial No. 10/051,320.

Claims 62-80 stand rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1 and 53 to 83 of co-pending application U.S. Serial No.: 10/681,418.

Claims 56-84 and 86-89 stand rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1 to 10 of U.S. Patent No. 6,683,061.

Claims 56-79, 81-84 and 86-89 stand rejected under the judicially created doctrine of obviousness-type double patenting for allegedly being unpatentable over the pending claims of co-pending US Application No. 10/048,033. Although the conflicting claims are not identical, they are not patentably distinct from each other because the compounds and the methods of treatment are overlapping with the instant claimed subject matter.

Claims 56-79, 81-84 and 86-89 of this application conflict with claims 1-30 of co-pending US Application No. 10/119,927 claims 1-22 of co-pending US Application No. 10/051,320, claims 1 and 53-83 of co-pending US Application No. 10/681,418, and of the pending claims of co-pending US Application 10/048,033.

Applicants respectfully defer responding to the above-noted objections until patentable subject matter has been indicated in the subject application.

III. CONCLUSION

No fees, other than the fee for processing of the RCE is considered necessary in connection with the filing of this Amendment and Response. However, if the Patent Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 50-2518**, referencing billing number **7008263002**.

However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account. Should a telephone advance prosecution of the subject application, the Examiner is invited to contact the undersigned at (650) 849-4950.

DATE: May 25, 2005

Respectfully submitted,

By: _____
Antoinette F. Konski
Registration No.: 34,202

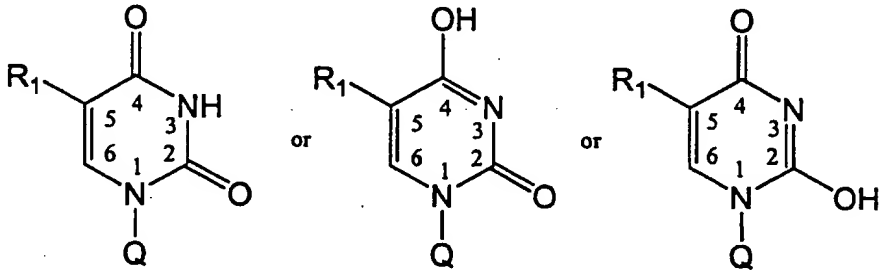
Bingham McCutchen, LLP
Three Embarcadero Center, Suite 1800
San Francisco, California 94111
Telephone: (650) 849-4950
Telefax: (650) 849-4800

CLAIMS

What is claimed is:

1. A method for selectively inhibiting a pathological cell, wherein the cell is characterized by overexpression of an endogenous, intracellular activating enzyme and wherein the enzyme is not inactivated by a substrate prodrug compound, the method comprising contacting the cell with an effective amount of the substrate compound having the structure selectively converted to a toxin in the cell by the activating enzyme, thereby selectively inhibiting the proliferation of the pathological cell.

2.

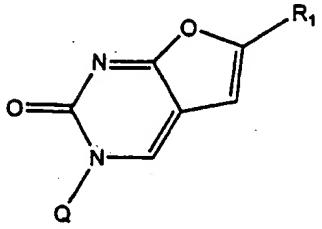
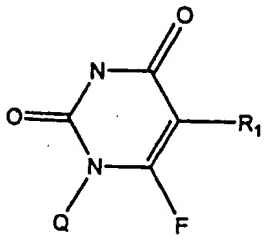
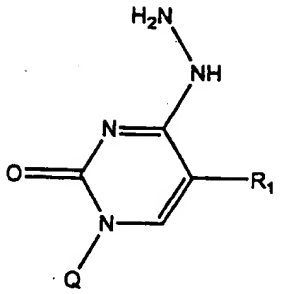


wherein R_1 is or contains a leaving group which is a chemical entity that has a molecular dimension and electrophilicity compatible with extraction from the pyrimidine ring by the activating enzyme, and which upon release from the pyrimidine ring activating enzyme, has the ability to inhibit the proliferation of the cell or kill the cell;

wherein Q is selected from the group consisting of a sugar, a carbocylic, an acyclic compound, and masked phosphate or phosphoramidate derivatives thereof and any 2, B.

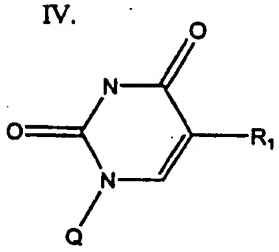
3. The method of claim 1 or 2, wherein the compound has the structure:

I. or II. or III.

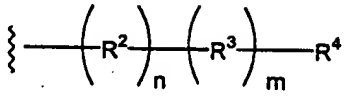
or

IV.



wherein:

R^1 is a moiety of the formula:



with the proviso that in compound I, n can be 0.

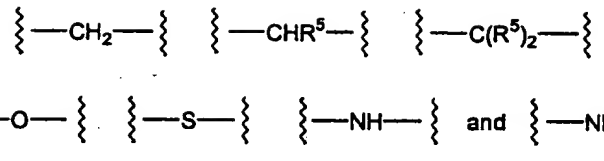
R^2 is a divalent electron conduit moiety selected from the group consisting of:

an unsaturated hydrocarbyl group;

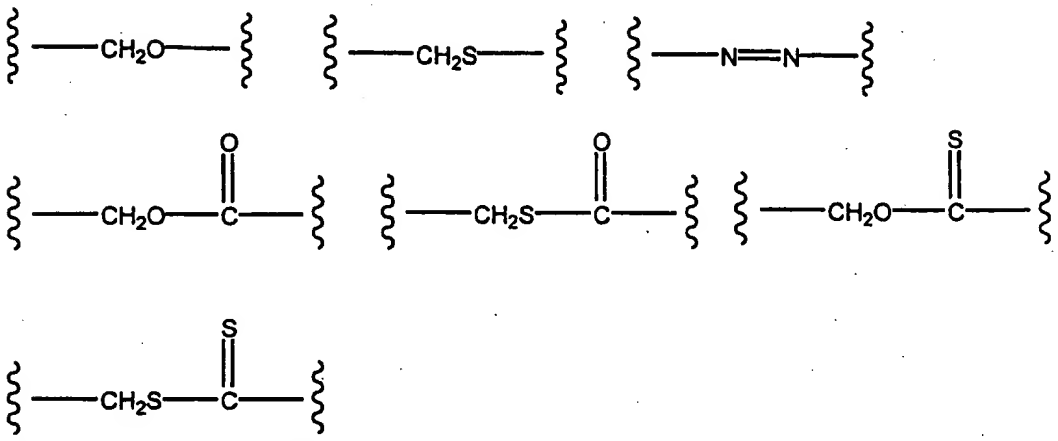
an aromatic hydrocarbyl group comprising one or more unsaturated hydrocarbyl groups; and,

a heteroaromatic group comprising one or more unsaturated hydrocarbyl groups;

R^3 is a divalent spacer moiety selected from the group consisting of:



and

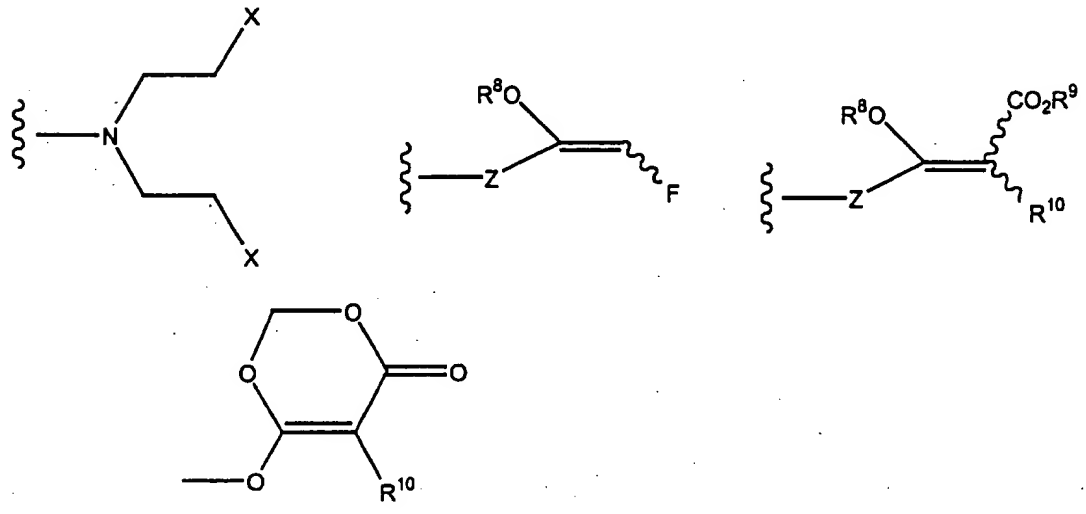


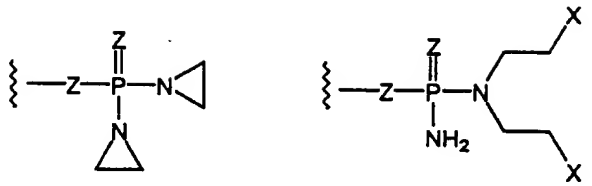
R^5 may be the same or different and is independently a linear or branched alkyl group having from 1 to 10 carbon atoms, or a cycloalkyl group having from 3 to 10 carbon atoms, or a halogen (F, Cl, Br, I);

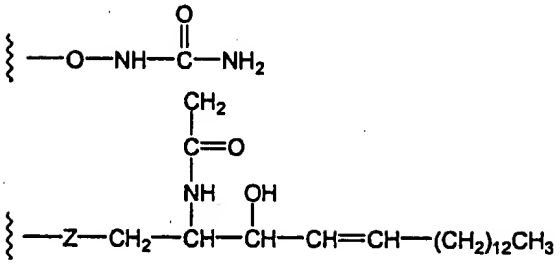
n is an integer from 0 to 10;

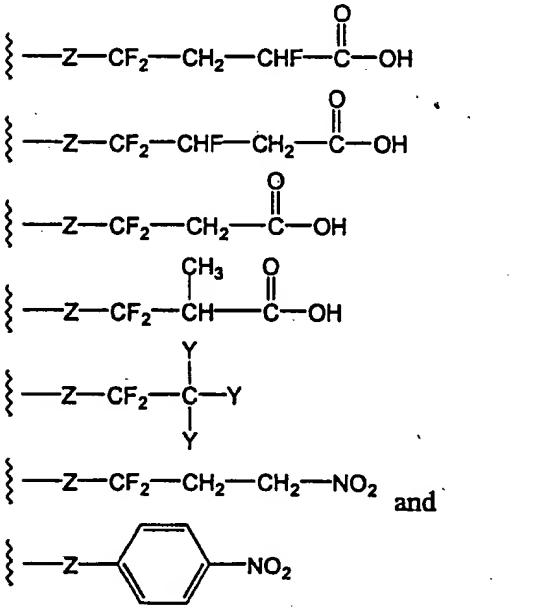
m is 0 or 1;

R^4 is a toxophore moiety selected from the group consisting of:









and

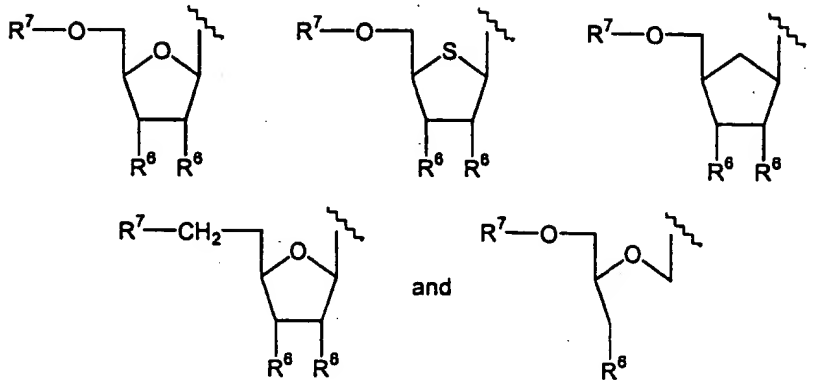
R^8 and R^9 are lower alkyls and R^{10} is H or CH_3

X is -Cl, -Br, -I, or other potent leaving group, with the proviso that when R^7 is -H, and m is zero, then R^4 is not a halogen or when m is zero and n is zero, then R^4 is not a halogen;

Y is independently -H or -F;

Z is independently -O- or -S-;

Q is a moiety selected from the group consisting of:



R^6 is independently -H, -OH, -OC(=O)CH_3, F, or other protected hydroxyl group; and,

R^7 is hydrogen, a phosphate group, a phosphodiester group, or a phosphoramidate group;

and wherein said compound may be in any enantiomeric, diasteriomeric, or stereoisomeric form, including, D-form, L-form, α-anomeric form, and β-anomeric form.

4. The method of claim 1, wherein the pathological cell overexpresses the activating enzyme as a result of loss of tumor suppressor function.

5. The method of claim 1, wherein the activating enzyme is overexpressed as a result of prior chemotherapy.

6. The method of claim 5, wherein the chemotherapy is fluoropyrimidine or Tomudex.

7. The method of claim 1, wherein the cell is a hyperproliferative or neoplastic cell.

8. The method of claim 7, wherein the neoplastic cell is a cell selected from the group consisting of a gastric cancer cell, a breast cancer cell and a colon cancer cell.

9. The method of claim 1, wherein the activating enzyme is thymidylate synthase.

10. The method of claim 1, wherein the activating enzyme is selected from the group consisting of thymidylate synthase, tyrosine kinase or dihydrofolate reductase.

11. The method of claim 1, wherein the cell and the activating enzyme are of the same species.

12. The method of claim 1, further comprising contacting the cell with a second therapeutic agent.

13. The method of claim 1, wherein the second agent is fluoropyrimidine or tomudex.

14. The method of claim 1, wherein the contacting is *in vitro*, *ex vivo* and *in vivo*.

15. The method of claim 1, wherein the contacting is *in vivo*.

16. The method of claim 1, wherein the activating enzyme is overexpressed at least 4 fold.

17. The method of claim 1, further comprising contacting the cell with an effective amount of a compound that diminishes intracellular thymidine or purine.

18. The method of claim 1, further comprising contacting the cell with an effective amount of 6-mercaptopurein, thioguanine, or 2'-deoxycoformycin.

19. The method of any of claims 1-18, wherein the compound is (e)-5-(2-bromovinyl)-2'-deoxy-5'-uridyl phenyl L-alaninylphosphoramidate.

20. A method for screening for prodrugs selectively converted to a toxin in a cell by an endogenous, intracellular enzyme that is not inhibited nor inactivated by the prodrug, comprising contacting a candidate prodrug with at least two test cells that express an endogenous, intracellular enzyme from the same or different species and assaying for activation of the prodrug into toxic agents by the endogenous, intracellular enzyme.

21. The method of claim 20, wherein one test cell is a normal cell and the other test cell is a pathological cell.

22. The method of claim 21, wherein the assay comprises analysis of intracellular metabolites by mass spectrometry.

23. The method of claim 20, wherein the candidate agent comprises a detectable agent.

24. The method of claim 23, wherein the detectable agent is a fluorescent marker.

25. The method of claim 20, wherein at least one test cell is a hyperproliferative or neoplastic cell.